REMARKS

Applicants' attorney thanks the Examiner for the courtesy of the recent telephonic interview conducted on November 9, 2004 during which the following issues and claim amendments were discussed.

Information Disclosure Statements

According to the Examiner, the references cited in the IDSs filed on February 22, 2002 and July 1, 2002 have not been received. Copies of each reference not initialed by the Examiner on the enclosed 1449 forms are enclosed as Appendix J. Applicants respectfully request the Examiner to consider the enclosed references and initial the 1449 forms accordingly.

Claim Amendments

Pending claims 56-78 have been canceled without prejudice and replaced with claims 79-99. Specifically, new claims 79-93 correspond to the subject matter of elected claims 56-71 (human monoclonal antibodies). Support for new claims 79-93 can be found at least in the following portions of the specification as originally filed:

New Claims	Support
79	Previously pending claim 69; and at page 10, lines 20-35, of the specification
80	Previously pending claim 68; and in Figure 13 of the specification
81	Previously pending claim 70; and at page 12, lines 9-16, of the specification
82	Previously pending claim 56; and at page 3, line 14, of the specification
83	Previously pending claim 60; and at page 3, lines 4-8, of the specification
84	Page 3, lines 16-17, of the specification
85	Previously pending claim 56; and at page 66, line 20 through page 67, line 27, of the specification
86	Page 3, lines 16-17, of the specification

87	Previously pending claim 58; and at page 64, lines 18-20, of the specification
88	Page 3, lines 11-12, of the specification
89	Original claim 12; Previously pending claim 62; and at page 2, lines 27-29, of the specification
90	Original claim 12; and at page 2, lines 27-29, of the specification
91	Original claim 15; previously pending claim 63; and at page 2, lines 29-31, of the specification
92	Original claim 38; and at page 5, lines 7-16, of the specification
93	Page 3, lines 16-17, of the specification

The foregoing amendments should in no way be construed as acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed or as previously pending in this or in one or more separate applications. No new matter has been added.

Rejection of Original Claims 56-63, 70 and 71 Under 35 U.S.C. §112, Second Paragraph

Original claims 56-63, 70 and 71 are rejected as being indefinite for the following reasons. Each of the issues raised by the Examiner, as it pertained to original claims 56-78, is addressed below.

With respect to original claim 56, the Examiner states that, at line 5, the claim should properly read "than" instead of "that." This typographical error is not present in the newly added claims. Therefore, this rejection is now moot.

Original claim 56 is further rejected based on the phrase "enhances the presentation of the antigen." In particular, the Examiner states that this phrase is a comparative phrase and "does not recite what antigen presentation is enhanced in comparison to." Applicants respectfully disagree. However, to expedite prosecution, the phrase objected to by the Examiner (as recited in new claim 85) specifies that the antibody or portion thereof, "when linked to an antigen, enhances presentation of the antigen by human dendritic cells following binding to the cells in that "the targeted antigen is processed and presented more efficiently compared to the

same antigen when not linked to the antibody." Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

With respect to the germline designations "V_H 5-51" and "V_K L15," the Examiner states that "they appear to comprise undefined laboratory designations." The Examiner further states that "the recitation of an antibody comprising genes is nonsensical as an antibody is a protein and genes are DNA, thus, an antibody cannot comprise a gene."

Applicants respectfully disagree. The nomenclature and characteristics (including sequences) of the V_H 5-51 and V_K L15 germline designations, referred to in new claim 81, were well-known in the art at the time the present application was filed. Indeed, the names and sequences of these genes were known and publicly available, for example, in the VBASE database (http://www.mrc-cpe.cam.ac.uk/), as well as in Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., *et al.* (1992) "The Repertoire of Human Germline V_H Sequences Reveals about Fifty Groups of V_H Segments with Different Hypervariable Loops" *J. Mol. Biol.* 227:776-798 (enclosed as Appendix A), and Cox, J. P. L. *et al.* (1994) "A Directory of Human Germ-line V_H Segments Reveals a Strong Bias in their Usage" *Eur. J. Immunol.* 24:827-836 (enclosed as Appendix B). These publications clearly demonstrate that reference to such germline nomenclature is not an arbitrary designation. Rather, the V_H 5-51 and V_K L15 gene designations have well-known art-recognized meanings, referring to particular human heavy and light chain immunoglobulin genes, the sequences of which are also well-known in the art.

With reference to new claim 81, Applicants also note that this claim refers to an isolated human monoclonal antibody, or antigen binding portion thereof, comprising a heavy chain variable region which is the product of a human germline V_H 5-51 gene and a light chain variable region which is the product of a human germline V_K L15 gene (see, *e.g.*, page 12, lines 13-20). Accordingly, the Examiner's comment concerning the inability of an antibody to comprise a gene is now moot.

Rejection of Original Claims 56-71 Under 35 U.S.C. §112, First Paragraph

Original claims 56-71 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled. In particular, the Examiner states that:

> [i]t is apparent that the antibody designated B11 is required to practice the claimed invention. As a required element, it must be known and readily available

to the public or obtainable by a repeatable method set forth in the specification. A deposit may be made under the provisions of the Budapest Treaty; an affidavit or declaration to that effect is required.

Applicants respectfully traverse this rejection. The claims (as amended) are drawn to an isolated human antibody (or antigen binding fragment thereof) that binds to human dendritic cells and comprises a particular variable region heavy and light chain sequences, *e.g.*, particular CDR and variable full-length region sequences, or variable regions derived from specific human germline gene sequences, *i.e.*, those known as V_H 5-51 and V_K L15. Based on Applicants' teachings in the present specification, combined with the knowledge and level of skill in the art, the claimed invention is fully enabled without the need to deposit antibody B11.

The factors to be considered when determining whether the claimed subject matter is enabled (*i.e.*, whether undue experimentation would be required to make or use the claimed invention) include, *inter alia*, the amount of direction or guidance presented in the specification, the state of the prior art and the relative skill of those in the art and the predictability in the art. *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

In the instant application, detailed guidance is provided in the specification regarding how to produce the claimed human antibodies (or antigen binding fragments thereof) that bind to human dendritic cells (see, *e.g.*, page 18, line 19 through page 20, line 32; page 23, line 24 through page 30, line 22; and Example 1 at pages 53-55). Methods for assaying the binding characteristics of such antibodies (see, *e.g.*, page 21, line 1 through page 22, line 10; and Example 2 at pages 56-62), as well as methods for characterizing the functions of such antibodies (*e.g.*, phagocytic and cell killing activities; page 22, line 12 through page 23, line 22; and Example 4 at pages 65-67), are also described in detail.

Furthermore, at the time of the present invention it was well-known how to graft antibody variable regions (*e.g.*, DNA fragments encoding the V_H and V_L segments) onto a wide variety of heavy and light chain frameworks, including not only those from which the original variable region came from, but also other known frameworks, to generate functionally equivalent antibodies. The techniques for doing so and the variety of suitable framework and constant regions that could have been used were well-known.

In particular, it was well-known in the art that antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs.

Because CDR sequences are responsible for most antibody-antigen interactions, it was also known that recombinant antibodies which mimic the properties of specific naturally occurring antibodies could be generated by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from any number of antibodies (see, *e.g.*, Riechmann, L. *et al.* (1998) *Nature* 332:323-327 (enclosed as Appendix C); Jones, P. *et al.* (1986) *Nature* 321:522-525 (enclosed as Appendix D); Queen, C. *et al.* (1989) *Proc. Natl. Acad. See. U.S.A.* 86:10029-10033 (enclosed as Appendix E); U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*).

In this regard, it was well-known that DNA fragments encoding the V_H and V_L segments of a particular antibody can be further manipulated by standard recombinant DNA techniques to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a V_L- or V_H-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region and/or a flexible linker. For example, with respect to the DNA encoding the V_H region, this DNA can be converted to a full-length heavy chain gene by operatively linking the V_H-encoding DNA to another DNA molecule encoding human heavy chain constant regions (CH1, CH2 and CH3). The sequences of such human heavy chain constant region genes were also well-known in the art (see *e.g.*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions were readily obtainable by standard PCR amplification. For example, the heavy chain constant region can be, *e.g.* an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. For a Fab fragment heavy chain gene, the V_H-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

Similarly, it was also known that the isolated DNA encoding the V_L region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the V_L-encoding DNA to another DNA molecule encoding the human light chain constant region, CL. The sequences of human light chain constant region genes were also known in the art (see *e.g.*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions were readily obtainable by standard PCR

amplification. For example, the light chain constant region can be, *e.g.*, a kappa or lambda constant region.

Moreover, to create a scFv gene, as taught in the present specification (for example, in Figure 9 and at page 11, lines 10-19), the V_H- and V_L-encoding DNA fragments can be operatively linked to another fragment encoding a flexible linker, *e.g.*, encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$, such that the V_H and V_L sequences can be expressed as a contiguous single-chain protein, with the V_H and V_L regions joined by the flexible linker (see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426 (enclosed as Appendix F); Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883 (enclosed as Appendix G); McCafferty *et al.*, (1990) *Nature* 348:552-554 (enclosed as Appendix H)).

As evidenced by the techniques discussed in the foregoing references, methods for producing antibodies by grafting variable regions onto various heavy and light chain frameworks were well developed at the time of the present invention. Accordingly, one of ordinary skill in the art could have predictably combined these methods with the sequence information provided by the present specification to have generated human antibodies that bind to human dendritic cells and include the recited CDRs or which are the product of the recited germline sequences, notwithstanding, the nature of their constant region.

Overall, it is clear that, once provided with the CDR or variable region sequences of a given human antibody, there was a high level of skill and a high level of predictability in the art at the time of the invention with respect to generating functionally equivalent antibodies. Thus, one of ordinary skill in the art would have been able to have made human antibodies having the claimed functions and heavy and light chain variable regions without undue experimentation and without the need for depositing antibody B11.

Rejection of Original Claims 56-71 Under 35 U.S.C. §112, First Paragraph

Original claims 56-71 are rejected under 35 U.S.C. §112, first paragraph, as being "new matter." The Examiner states that the specification and the claims as originally filed do not provide support for the antibodies as set forth below.

Reasons (A) and (B)

The Examiner states that the specification does not support:

(A) An isolated human monoclonal antibody, or antigen-binding portion thereof, that has the following properties:

a) the antibody binds to human dendritic cells;
b) the antibody binds to human macrophages but to a lesser extent than the binding to human dendritic cells;
c) the antibody inhibits dextran uptake by human dendritic cells;
d) the antibody is internalized following binding to human dendritic cells; and
e) the antibody, when conjugated to an antigen, enhances presentation of the antigen by human dendritic cells (Claim 56), and

(B) Claims 57-63 and 70 which depend from claim 56.

Applicants respectfully traverse this rejection. However, to expedite prosecution, the claims as amended no longer encompass "any antibody that might comprise the recited properties," as objected to by the Examiner. Instead, and as described above, the claims are drawn to particular antibodies and fragments thereof with specific structural and functional characteristics (see, independent claims 79-81). Accordingly, this rejection is moot.

Reason (C)

The Examiner further states that the specification and the claims as originally filed do not provide support for "the antibody of Claim 56 . . . with a binding affinity of at least about 10^8 M^{-1} (Claim 61) . . . "

Applicants respectfully traverse this rejection. Support for an antibody, or binding portions thereof, with a binding affinity of at least about 10^8 M^{-1} can be found throughout the specification as originally filed, for example, at page 3, lines 4-8. Further, this binding affinity is now recited in new claim 83, which depends from new independent claim 79. As pointed out immediately above, independent claim 79 no longer encompasses "any antibody that might comprise the recited properties," as objected to by the Examiner. In particular, new independent claim 79 is drawn to a particular antibody, or binding fragments thereof, with specific structural and functional characteristics which are fully supported by the specification. Therefore, the claims do not encompass new matter.

Reason (D)

The Examiner further asserts that the specification and the claims as originally filed do not provide support for "the antibody of Claim 56 . . . which is an antibody fragment (Claim 63)."

Applicants respectfully traverse this rejection. Support for antibody fragments, *e.g.*, a single chain antibody or an Fab' fragment, can be found throughout the specification as originally filed. For example, support can be found in original claim 15, previously pending claim 63, and at page 2, lines 29-31. Further, this limitation is now recited in new claim 91, which depends from new independent claim 79. As pointed out immediately above, independent claim 79 no longer encompasses "any antibody that might comprise the recited properties," as objected to by the Examiner. In particular, new independent claim 79 is drawn to a particular antibody, or binding fragment thereof, with specific structural and functional characteristics that are fully supported by the specification. Therefore, the claims do not encompass new matter.

Reason (E)(1)

The Examiner further asserts that previously pending claims 67-70 which are drawn to antibodies comprising V_L and V_H regions having the amino acid sequences shown in SEQ ID NOs:2 and 4 add new matter.

Applicants respectfully traverse this rejection. Antibodies, or binding portions thereof, which comprise the human heavy chain variable region, SEQ ID NO:4, and the human light chain variable region, SEQ ID NO:2, are clearly supported by the specification (see, *e.g.*, Figure 13 of the specification). Further, Applicants refer to their discussion set forth above (the substance of which is reiterated here) regarding the detailed description provided in the present specification and the considerable knowledge in the art at the time of the invention concerning how to generate antibodies having a variety of constant regions but sharing the same variable region and having the same functional characteristics. Applicants also refer to their own teachings contained in the present specification (and described in detail above) for generating and testing such antibodies. Based at least on the foregoing, Applicants respectfully request the Examiner to withdraw this rejection.

Reason (E)(2)

The Examiner also contends that antibodies which comprise sequences which are at least 80% homologous to SEQ ID NOs:2 and 4 are not supported by the specification and the claims as originally filed.

Applicants respectfully traverse this rejection. However, to expedite prosecution, the amended claims do not refer to homologous sequences. Therefore, this rejection is moot.

Reason (E)(3)

The Examiner further asserts that antibodies which comprise the CDRs contained within SEQ ID NOs:2 and 4 are new matter. In particular, the Examiner states that:

> the disclosure of a genus (SEQ ID NOs:2 and 4) is insufficient support for claims drawn to a subgenus (the CDR fragment of SEQ ID NOs:2 and 4). Even regarding claims 68, wherein the entire SEQ ID NOs:2 and 4 are recited, the specification cannot support antibodies comprising *any* other constant regions.

Applicants respectfully traverse this rejection. First, the claimed CDRs do not constitute "a subgenus" of the full-length variable regions shown in SEQ ID NOs:2 and 4. Rather, these CDRs constitute an inherent and recognizable portion of a variable region.

Specifically, the presently claimed CDRs are present in the full-length variable regions provided in SEQ ID NOs:2 and 4, as originally filed. These CDRs were readily identifiable by one of ordinary skill in the art at the time of filing using standard mapping techniques. For example, by using the Kabat and the Clothia numbering schemes (widely adopted standards in the art at the time of filing) the CDRs and constant regions could have been determined simply by reviewing the sequence information provided by Applicants, *e.g.*, by plugging this sequence information into a computer program, such as, *e.g.*, SUBIM (a program for analyzing the Kabat database and determining the variability subgroup of a new immunoglobulin sequence, S. Deret, C. Maissiat, P. Aucouturier and J. Chaomillier, CABIOS, vol. 11, no. 4, 1995, Pages 435-439; enclosed as Appendix I), which automatically identifies the CDRs and constant regions. Therefore, the CDRs recited in claim 79 do not constitute new matter. They are a readily identifiable feature of the full-length variable regions, as originally filed.

Based at least on the foregoing, Applicants respectfully request the Examiner to withdraw this rejection.

Reason (F)

The Examiner also states that antibodies which comprise the sequences derived from human germline sequences V_H 5-51 and V_K L15 are new matter.

Applicants respectfully disagree. Applicants refer to their discussion set forth above (the substance of which is reiterated here) regarding the detailed description provided in the present specification and the considerable knowledge in the art at the time of the invention concerning the V_H 5-51 and V_K L15 germline designations. Such designations were well-known in the art at

the time the present application was filed. The names and sequences of these genes were known and publicly available.

Based at least on the foregoing, the claims do not include new matter.

Rejection of Original Claims 56-71 Under 35 U.S.C. §112, First Paragraph

Original claims 56-71 are rejected under 35 U.S.C. §112, first paragraph, as not meeting the written description requirement. Specifically, the Examiner states that:

> [t]here is insufficient written description to show that Applicant was in possession of: (a) an isolated human monoclonal antibody comprising the functional limitations of claims 56-63, except the B11 antibody, nor any fragments thereof; (b) an isolated human monoclonal antibody comprising conservative modifications of the antibodies of claims 64-66; and (c) an isolated human monoclonal antibody at least 80% homologous to the antibody of claims 67.

The Examiner concludes that:

> in its entirety, the specification discloses just a single example of several essentially unlimited genuses. Given the essentially unlimited number of antibodies encompassed by the claims, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genuses. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

Applicants respectfully traverse this rejection. However, to expedite prosecution, the claims have been amended to encompass an isolated human antibody (or antigen binding fragment thereof) that binds to human dendritic cells and comprises a particular structure, *e.g.*, particular CDR or full-length variable region sequences, or variable regions which are the products of specific human germline gene sequences, *i.e.*, those known as V_H 5-51 and V_K L15. Accordingly, the claims no longer encompass an "unlimited number of antibodies," as stated by the Examiner. Instead, the claims are drawn to particular antibodies and fragments thereof having particular structural and functional characteristics which are described in detail in the specification such that one of ordinary skill in the art would recognize that Applicants had possession of the claimed invention at the time of filing.

Accordingly, based on the standards set forth in the Written Description Guidelines, a person skilled in the art would recognize in the present specification a description of the claimed invention upon consideration of Applicants' teachings contained in the specification and the knowledge and level of skill in the art.

Rejection of Original Claims 63-67 Under 35 U.S.C. §112, First Paragraph

Original claims 63-67 are rejected under 35 U.S.C. §112, first paragraph, as not being enabled. The Examiner states that:

> [g]iven the established unpredictability of the art, the instant specification would require a significant teaching to be enabled. In particular, it is unlikely that the antibody fragments, conservatively modified antibodies, or 80% homologous antibodies encompassed by the claims could function for their intended use. Note that the fragments and antibodies of the claims would encompass fragments and antibodies modified in the CDR binding regions of the antibodies. It is well-established that even a single substitution in the CDR regions of an antibody can have a dramatic, and unpredictable, effect on antibody binding (and, thus, function). See, for example, Kobayashi *et al.* (1999) wherein it is taught that even single conserved substitutions can have a large effect on antibody binding (see Figure 4; note the log scale). Note the breadth of the claims; the fragments and modified antibodies of the claims are not limited in the number of modifications in which *all* of the amino acids are changed would be encompassed by the claims . . .

Applicants respectfully traverse this rejection. However, to expedite prosecution, claims 63-67 have been canceled. New claims 79-83 do not contain reference to conservative sequence

modification or sequences which are 80% homologous to the specified SEQ ID NOs. Accordingly, this rejection is now moot.

SUMMARY

In view of the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call (617) 227-7400.

Applicants believe no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 12-0080, under Order No. MXI-166 from which the undersigned is authorized to draw.

Dated: 3 May 05

Respectfully submitted,

By _____

Jeanne M. DiGiorgio
Registration No: 41,710
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney For Applicants